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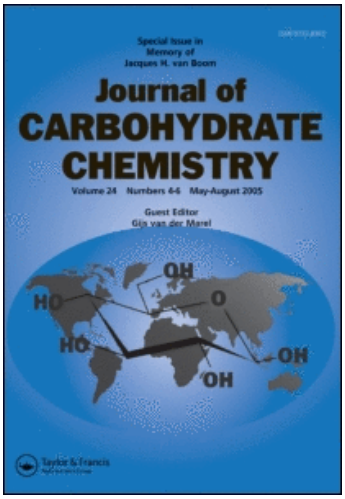

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Synthesis of (4*R*,5*S*)-(-)- and (4*S*,5*S*)-( )-L-Factors and Muricatacin from D-Glucose

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COMMUNICATION

SYNTHESIS OF (4*R*, 5*S*)-(-)- AND (4*S*,5*S*)-(+)-L-FACTORS AND MURICATACIN FROM D-GLUCOSE

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In connection with our projects on the synthesis of biologically active 5-hydroxyalkan-4-olides which have a chiral 2,3-diol unit,[1] we have carried out the synthesis of (4*R*,5*S*)-(-)- and (4*S*,5*S*)-(+)-L-factors (**1**),[2] the proposed autoregulators from Streptomyces griseus, and muricatacin (**2**),[3] a biologically active constituent from the seeds of Annona muricata L. *via* 2,3-dihydroxy aldehydes derived from D-glucose.

Hex-3-enofuranose **4** was prepared by the elimination of the triflate derived from 3-hydroxy furanose **3**,[4] which in turn was synthesized[5] from D-glucose (Scheme 1). Hydroboration of **4** with disiamylborane[6] followed by oxidation with H_2O_2/NaOH afforded 3-hydroxy-β-threohexofuranose **5**,[7] $[\alpha]_D^{25}$ -16.7° (*c* 1.73, $CHCl_3$) as the only isolated product in 56% yield after column chromatographic purification. The stereochemistry of the *n*-pentyl- and hydroxy- substituent of **5** was confirmed by the ^1H NMR spectrum and capillary GLC data.[4] Removal of the isopropylidene group in **6** which was prepared from **5**, with 2 N HCl provided the hemiacetal, which was subjected to oxidative cleavage with sodium periodate to afford (2*S*,3*S*)-2-benzyloxy-3-formyloxy-1-octanal **7**,[8] $[\alpha]_D^{25}$ -44.1° (*c* 0.50, $CHCl_3$). Horner-Emmons olefination of the aldehyde (2*S*,3*S*)-**7** with the anion of triethylphosphonoacetate gave the (*E*)-unsaturated ester **8**[7] in 90% yield. Catalytic hydrogenation followed by treatment of trifluoroacetic acid afforded (4*R*,5*S*)-(-)-5-hydroxy-4-decanolide (**1**),[8,9] $[\alpha]_D^{25}$ -10.1° (*c* 2.0, $CHCl_3$) in 63% overall yield from **7**.

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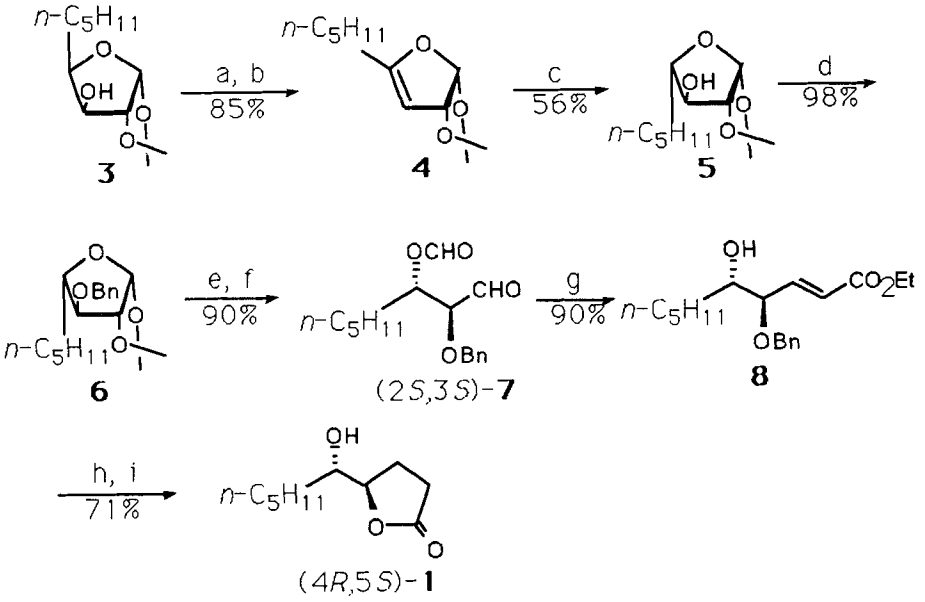
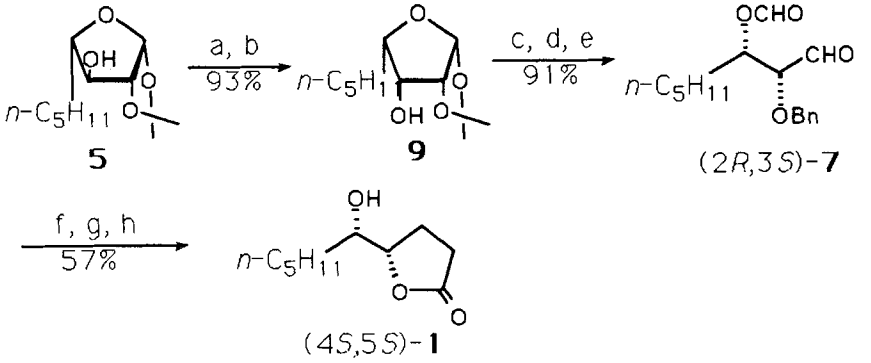


a) Tf_2O, pyridine, CH_2Cl_2, -10 °C, 1 h b) DBU, ether, rt, 5 h c) Sia_2BH, THF, 0 °C→rt; H_2O_2/ NaOH, 24 h d) NaH, BnCl, THF, rt, 6 h e) 2 N HCl, DME, rt, 24 h f) $NaIO_4$, MeOH, rt, 1 h g) NaH, THF, $(EtO)_2POCH_2CO_2Et$, rt, 24 h h) H_2, Pd/C, EtOAc, rt, 20 h i) TFA/ H_2O (4 : 1), rt, 1 h

Scheme 1



a) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -60 °C→ rt, 1 h b) $NaBH_4$, MeOH, -78 °C, 12 h c) NaH, BnCl, THF, rt, 5 h d) 2 N HCl, DME, rt, 24 h e) $NaIO_4$, MeOH, rt, 1 h f) NaH, THF, $(EtO)_2POCH_2CO_2Et$, rt, 20 h g) H_2, Pd/C, EtOAc, rt, 24 h h) TFA/ H_2O (4:1), rt, 1 h

Scheme 2

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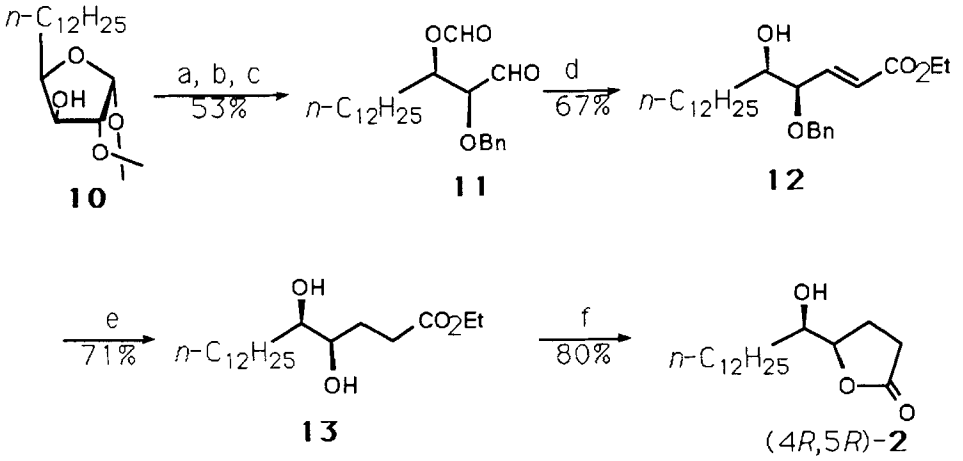

a) NaH, BnCl, THF, rt, 5 h b) 2 N HCl, DME, rt, 48 h c) $NaIO_4$, MeOH, rt, 1 h d) NaH, $(EtO)_2POCH_2CO_2Et$, THF, rt, 3 h e) H_2, Pd/C, EtOAc, rt, 24 h f) TFA/H_2O(4:1), rt, 3 h

Scheme 3

The (4*S*, 5*S*) diastereomer of **1** was synthesized by a similar route (Scheme 2). The β-3-hydroxy- group in **5** was converted to an α-hydroxy group by Swern oxidation of **5** followed by reduction with $NaBH_4$ in MeOH at -78 °C to afford **9**[7] as the only isolated product.[4] Benzylation of **9** gave the benzyloxy compound, which was converted to (2*S*,3*R*)-2-benzyloxy-3-formyloxy-1-octanal **7**,[8] $[\alpha]_D^{25}$ -25.9° (*c* 1.42, $CHCl_3$) in 91% overall yield from **9**. Emmons olefination of the aldehyde (2*S*,3*R*)-**7** with the anion of triethylphosphonoacetate followed by catalytic hydrogenation and lactonization afforded (4*S*,5*S*)-**1**,[8,9] mp 42 °C, $[\alpha]_D^{25}$ + 31.4° (*c* 5.0, $CHCl_3$) in 57% overall yield.

Recently, a simple, biologically active constituent isolated from the seeds of Annona muricata L. was identified[3] as (4*R*, 5*R*)-5-hydroxy-4-heptadecanolide (**2**) and named as muricatacin. We report here the first synthesis of muricatacin (**2**) using (2*S*,3*R*)-*O*-protected 2,3-dihydroxy aldehyde **11**[7] (Scheme 3). 3-Hydroxy furanose **10**[10] was converted to (2*S*,3*R*)-**11**,[8] mp 53-55 °C, $[\alpha]_D^{25}$ +2.86° (*c* 2.1, $CHCl_3$) by benzylation of **10** followed by deprotection and oxidative cleavage. Reaction of the aldehyde **11** with the anion of triethylphosphonoacetate provided the condensed (*E*)-unsaturated ester **12**[7] in 67% after column chromatographic separation. Hydrogenation to **12** (71%) and treatment of **13** with aqueous trifluoroacetic acid afforded the (4*R*,5*R*)-lactone **2**[3,8] (muricatacin), mp 57-58 °C, $[\alpha]_D^{25}$ -18.8° (*c* 2.4, $CHCl_3$) in 56% yield from **12**.

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We thank Professor K. Mori (The University of Tokyo, Japan) for the ^1H NMR spectra of L-factors. Generous financial support by the Korea Science and Engineering Foundation -The Organic Chemistry Research Center is gratefully acknowledged.

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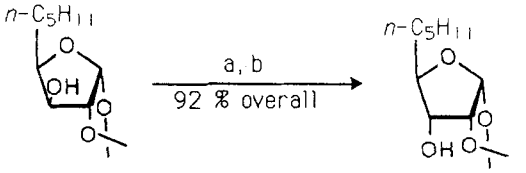
4. Capillary GC analyses were performed for **3**, **5**, **9** and **14** using a Hewlett Packard 5880 GC system (column : Supelcowax 10, 0.25 mm X 30 m, oven temp:120 °C → 200 °C, carrier gas : N_2, 1.0 ml / min, injection temp. : 250 °C). The values of the retention times for each compounds were as follows : **3** : 23.21 min, **5** : 25.87 min, **9** :16.64 min, **14** : 15.57 min. 3- Hydoxy furanose **14** was prepared from **3** as follows.



3 **14**

a)DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -60 °C → rt, 1 h b) $NaBH_4$, MeOH, -78 °C, 4 h.

5. S. K. Kang and H. S. Cho, *Tetrahedron Lett.*, 32, 367 (1991).

6. Hydroboraton with disiamylborane gave much better result than $BH_3 \cdot SMe_2$ in terms of yield and purity of the product.

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7. All new compounds gave spectral data (IR, ^{1}H- and ^{13}C-NMR) and satisfactory analytical data in accord with the assigned structures.

3: Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63
Found: C, 62.39; H, 9.74.

5: Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63
Found: C, 62.72; H, 9.81.

6: Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81
Found: C, 71.05; H, 8.72.

8: Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81
Found: C, 71.14; H, 9.07.

9: Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63
Found: C, 62.43; H, 9.92.

10: Anal. Calcd for $C_{19}H_{36}O_4$: C, 69.47; H, 11.05
Found: C, 69.72; H, 11.14.

11: Anal. Calcd for $C_{25}H_{42}O_4$: C, 73.85; H, 10.41
Found: C, 73.69; H,10.64

13: Anal. Calcd for $C_{19}H_{38}O_4$: C, 69.05; H, 11.59
Found: C, 68.89; H, 11.71.

(4*R*, 5*R*)-**2**: Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.79; H, 11.34
Found: C, 71.82; H, 11.43.

8. Selected spectral and physical data : (2*S*, 3*S*)−**7** : TLC , SiO_2, R_f = 0.76 (EtOAc/ hexanes = 1:1) ; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (t, 3H, $J_{Me,\ CH_2}$ = 7.2 Hz, $MeCH_2$), 1.10−1.40 (m, 6H, $3CH_2$), 1.55−1.90 (m, 2H, CH_2), 3.88 (dd, 1H, $J_{2,3}$ = 3.5 Hz, $J_{1,2}$ = 1.5 Hz, H-2), 4.72 (s, 2H, OCH_2), 5.34 (m, 1H, H-3), 7.35 (s, 5H, Ph), 8.08(s, 1H, OCHO), 9.72 (d, 1H, $J_{1,2}$ = 1.5 Hz, CHO); IR (neat) 2890, 2830 and 1725 cm^{-1} (aldehyde). (4*R*, 5*S*)−**1** : TLC, SiO_2, R_f = 0.29 (EtOAc/hexanes = 1:1); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.89 (t, 3H, J = 7.2 Hz, $MeCH_2$), 1.25−1.40 (m, 5H, $2CH_2$ and CH), 1.42 (m, 2H, 2CH), 1.50−1.60 (m, 1H, CH), 2.15 (dddd, 1H, J = 5.5, 7, 10, 12 Hz, H-3a), 2.28 (dddd, 1H, J = 7, 7, 10, 12 Hz, H-3b), 2.50 (ddd, 1H, J = 7, 10, 18 Hz, H-2a), 2.60 (ddd, 1H, J = 5.5, 10, 18 Hz, H-2b), 3.90 (m, 1H, H-5), 4.45 (ddd, 1H, J = 3, 7, 7 Hz, H-4) ; IR (neat) 3500 (OH), 1770 cm^{-1} (lactone). (4*R*, 5*R*)−**2** : mp 57 - 58 °C ; TLC, SiO_2, R_f = 0.28 (EtOAc / hexanes = 1:1) ; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 7 Hz, $MeCH_2$), 1.24−1.40 (m, 20H, $10CH_2$),

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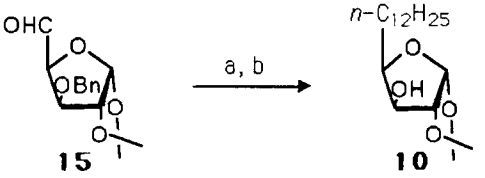
1.52–1.59 (m, 2H, CH_2), 1.92 (bs, 1H, OH), 2.13 (ddt, 1H, $J_{3a,4}$ = 8 Hz, $J_{3a,3b}$ = 13 Hz, H-3a), 2.24 (ddt, 1H, $J_{3b,4}$ = 8 Hz, H-3b), 2.55 (dt, 1H, $J_{2a,3a} = J_{2a,3b}$ = 10 Hz, $J_{2a,2b}$ = 18 Hz, H-2a), 2.63 (dt, 1H, $J_{2b,3a}$ = 10 Hz, $J_{2b,3b}$ = 5 Hz, H-2b), 3.57 (m, 1H, H-5), 4.42 (dt, 1H, $J_{3,4}$ = 7 Hz, $J_{4,5}$ = 5 Hz, H-4) ; IR (KBr) 3500 (OH), 1770 and 1210 cm^{-1}(ester) ; MS (*m/e*, CI) : 285 (MH^+), 267, 199, 180, 85 (base peak).

9. ^1H NMR (500 MHz) data of L-factors thus synthesized were identical with the data of the synthetic compounds provided by Professor K. Mori.

10. 3-Hydroxy furanose **10** was prepared from the known aldehyde **15**.



15 **10**

a) $CH_3(CH_2)_{10}P^+Ph_3Br^-$, n-BuLi, THF, rt, 12 h (86%) b) H_2, Pd/C, EtOAc, rt, 10 h (91%).

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